UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HORIZON PHARMA, INC. and POZEN INC.,	:	Case No. 11-2317 (MLC) (DEA)
	:	**REDACTED**
Plaintiffs,	:	**AMENDED MEMORANDUM OPINION** :
v.	:	
	:	
DR. REDDY'S LABORATORIES, INC., *et al.*,	:	
	:	
Defendants.	:	
_____	:	

COOPER, District Judge

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I. Background

This is a patent dispute between Plaintiffs Horizon Pharma, Inc. and Pozen Inc. (together, "Horizon") and two groups of generic drug manufacturers: (1) Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. ("DRL"); and (2) Mylan, Inc.; Mylan Pharmaceuticals Inc.; and Mylan Laboratories Ltd. ("Mylan," and together with DRL, "Defendants"). Horizon holds New Drug Application ("NDA") No. 022511 for Vimovo, a branded drug product whose active pharmaceutical ingredients are naproxen and esomeprazole magnesium. (Dkt. 421 at 6.)[1]

This case arises out of Defendants' submission of Abbreviated New Drug Applications ("ANDAs") to the FDA pursuant to the Hatch-Waxman Act, 21 U.S.C. § 355(j), for the purpose of obtaining FDA approval for the commercial manufacture, use, import, offer for sale, and sale of a generic version of Vimovo. Specifically, DRL filed ANDA No. 202461 ("DRL ANDA I") and ANDA No. 204206 (DRL ANDA II"). Mylan filed ANDA No. 204920 ("Mylan ANDA"). Based on submissions by the parties in the pre-trial order, all three ANDAs relate to tablets containing 375 mg or 500 mg of naproxen and 20 mg esomeprazole magnesium. (Dkt. 421 at 7–8.)[2] All three ANDAs included so-called "Paragraph IV" certifications that the products would not infringe Horizon's patents and/or that those patents are invalid or unenforceable. (Id.) The Paragraph IV certifications covered U.S. Patent No. 6,926,907 ("the '907 patent") and No. 8,557,285 ("the '285 patent")

[1] The Court will cite documents filed on the Electronic Case Filing System ("ECF") by referring to the docket entry numbers as "dkt." Pincites reference ECF pagination.

[2] Lupin Pharmaceuticals, Inc. and Lupin Ltd. ("Lupin") submitted an ANDA filing (No. 202654). Horizon's case against Lupin (Case No. 11-4275) has been stayed pending the outcome of this case. (Dkt. 455.)

(together, the "Asserted Patents"). In response to those Paragraph IV certifications, Horizon asserted infringement of claims 5, 15, 52, and 53 of the '907 patent.[3] Horizon has also asserted claims 1 through 4 of the '285 patent.[4]

Mylan has stipulated that its ANDA product would infringe the Asserted Patents. (Dkt. 421 at 8.) DRL has admitted that its DRL ANDA I Product would infringe the Asserted Patents. (Id.) We previously granted summary judgment in DRL's favor that its ANDA II

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[3] The asserted claims of the '907 patent (together with claim 1 for context) are:

1. A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:

(a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;

(b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms; and wherein said unit dosage form provides for coordinated release such that:

i) said NSAID is surrounded by a coating that, upon ingestion of said unit dosage form by said patient, prevents the release of essentially any NSAID from said dosage form unless the pH of the surrounding medium is 3.5 or higher;

ii) at least a portion of said acid inhibitor is not surrounded by an enteric coating and, upon ingestion of said unit dosage form by said patient, is released regardless of whether the pH of the surrounding medium is below 3.5 or above 3.5.

5. The pharmaceutical composition of claim 1, wherein said acid inhibitor is a proton pump inhibitor selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

15. The pharmaceutical composition of . . . claim[] 1 . . . wherein said acid inhibitor is a proton pump inhibitor.

51. A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of claim 15.

52. The method of claim 51, wherein said pain or inflammation is due to either osteoarthritis or rheumatoid arthritis.

53. The pharmaceutical composition of any one of claims 5-11 wherein said unit dosage form is a multilayer tablet comprising a single core and one or more layers outside of said single core, wherein:

i) said NSAID is present in said core;

ii) said coating that does not release said NSAID unless the pH of the surrounding medium is 3.5 or higher surrounds said core; and

iii) said acid inhibitor is in said one [or] more layers outside said core.

('907 patent at col. 20, line 9 to col. 24, line 6.)

Product does not infringe the '907 patent. (Dkt. 380). Accordingly, the only infringement dispute at trial was whether DRL's ANDA II Product infringes the '285 patent. Most of the trial was focused on Defendants' contentions that claims in the Asserted Patents are invalid under 35 U.S.C. § 103 and/or § 112.

We held a six day bench trial on those issues from January 12–20, 2017 and heard closing arguments on May 17, 2017.[5] We heard live testimony from seven witnesses. Dr. John Plachetka, called by Horizon, was the named inventor on the Asserted Patents. (Tr. 15–192.) Dr. David Metz, called by Defendants, was qualified as an expert in gastroenterology, including the treatment of acid peptic disorder. (Tr. 260–396.) Dr. Arthur Kibbe, called by Defendants, was qualified as an expert in pharmaceutical formulation and development. (Tr.

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[4] The asserted claims of the '285 patent are as follows:

1. A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:

(a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and

(b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher;

wherein said unit dosage form provides for release of said esomeprazole such that upon introduction of said unit dosage form into a medium, at least a portion of said esomeprazole is released regardless of the pH of the medium.

2. The pharmaceutical composition of claim 1, wherein naproxen is present in said unit dosage form in an amount of 200-600 mg.

3. The pharmaceutical composition of claim 1, wherein esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.

4. The pharmaceutical composition of claim 1, wherein naproxen is present in said unit dosage form in an amount of between 200-600 mg and esomeprazole in an amount of from 5 to 100 mg per unit dosage form.

('285 patent at col. 22, lines 8–28.)

[5] The trial transcript is separated into seven volumes, but the pages are numbered consecutively. (See dkt. 458 (Vol. 1), dkt. 461 (Vol. 2), dkt. 463 (Vol. 3), dkt. 466 (Vol. 4), dkt. 468 (Vol. 5), dkt. 471 (Vol. 6), and dkt. 491 (Vol. 7).) We will cite to the trial transcript using the designation "Tr." without indicating the specific volume.

408–565.) Dr. Michael Mayersohn, called by Defendants, was qualified as an expert on pharmacokinetics and pharmacodynamics. (Tr. 569–603; Tr. 610–707.) Dr. Robert Williams, III, called by Horizon, was qualified as an expert in pharmaceutical formulation. (Tr. 716–842; Tr. 849–1017.) Dr. David Taft, called by Horizon, was qualified as an expert in pharmacokinetics. (Tr. 1018–1102.) Dr. David Johnson, called by Horizon, was qualified as an expert in gastroenterology. (Tr. 1108–1266.) The parties also submitted designated deposition testimony from Brian Ault (DTX-1393); Mark Sostek (DTX-1396); Jeff Sherman (DTX-1397); Dennis McNamara (DTX-1398); Abhijit Desmukh (PTX-581); John Horn (PTX-582); T. Sudhakar Koudinya (PTX-583); Snehalatha Movva (PTX-584); and Badri Viswanathan (PTX-585).[6]

This opinion follows the parties' division of the relevant legal issues raised at trial and addresses the interrelated infringement and § 112 issues in Section III, infra, and the interrelated obviousness and § 112 issues in Section IV, infra. In support of their arguments, Horizon and Defendants submitted separate post-trial briefs on the issues addressed in Section III (dkt. 489-2; dkt. 489-3) and Section IV (dkt. 489; dkt. 489-1).

For the reasons below, we conclude that DRL's ANDA II Product infringes the '285 patent and that the asserted claims are not invalid under 35 U.S.C. § 103 and/or § 112. Accordingly, we will grant judgment in Horizon's favor and issue an appropriate order.

[6] Defendants object to Dr. Horn's deposition testimony as inadmissible hearsay. (Dkt. 472.) We conclude that Dr. Horn's testimony is admissible because it satisfies the requirements of the hearsay exception in Federal Rule of Civil Procedure 32(a) for deposition testimony of an unavailable witness. See Novozymes A/S v. Genencor Int'l, Inc., No. 05-160, 2006 WL 318936, at *1 (D. Del. Feb. 10, 2006). We note, however, that the exclusion of Dr. Horn's testimony would not have changed any of our conclusions in this opinion.

II. Legal Standards

A. Infringement

The standard for patent infringement is set forth in 35 U.S.C. § 271, which states that "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). The burden to prove infringement rests with the patentee who must prove infringement by a preponderance of the evidence. Medtronic, Inc. v. Mirowski Family Ventures, LLC, 134 S. Ct. 843, 846 (2014). To prove infringement, the patentee must show that an accused product is within the claim limitations of the patent-in-suit either literally or under the doctrine of equivalents. See Warner Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 21 (1997); Amgen Inc. v. F. Hoffman La Roche Ltd., 580 F. 3d 1340, 1374 (Fed. Cir. 2009). In a Hatch-Waxman case, the actual act of infringement is the filing of an ANDA to obtain approval to engage in the commercial manufacture, use, or sale of a patented drug or method of use. 35 U.S.C. § 271(e)(2). Specifically, § 271(e)(2)(A) provides that it shall be an act of infringement to submit an ANDA "if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent."

The infringement analysis is a two-step process in which we must: (1) determine the scope and meaning of the disputed patent claim terms; and (2) compare the properly construed claims to the allegedly infringing product or device. Advanced Steel Recovery, LLC v. X-Body Equip., Inc., 808 F.3d 1313, 1316 (Fed. Cir. 2015).

B. Written Description

A patent specification must contain "a written description of the invention." 35 U.S.C. § 112(a). To satisfy that requirement, "the specification must describe an invention understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed." Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010). "The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not." Amgen Inc. v. Hoechst Marion Roussel, 314 F.3d 1313, 1330 (Fed. Cir. 2003). The requirement thus mandates that the applicant "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561 (Fed. Cir. 1991).

The "hallmark of written description is disclosure," and the test for its sufficiency is "whether the disclosure . . . reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Ariad, 598 F.3d at 1351. "It is the specification itself that must demonstrate possession" and analysis of the adequacy of the written description "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." Id. at 1351–52. The disclosure must "allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 968 (Fed. Cir. 2002).

"There is no rigid requirement that the disclosure contain 'either examples or an actual reduction to practice.'" Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1308 (Fed.

Cir. 2015) (quoting Ariad, 598 F.3d at 1352). Rather, "the proper inquiry is whether the patentee has provided an adequate description that 'in a definite way identifies the claimed invention' in sufficient detail such that a person of ordinary skill would understand that the inventor had made the invention at the time of filing." Id. at 1308. Moreover, "an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention." See Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003). The challenging party must show lack of adequate written description by clear and convincing evidence to rebut the patent's presumption of validity. Alcon Research Ltd. v. Barr Labs., Inc., 745 F.3d 1180, 1188–91 (Fed. Cir. 2014).

C. Enablement / Utility

35 U.S.C. § 112 requires applicants to describe the manner of making and using the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same . . . ." The Federal Circuit has explained that "the how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention." Rasmusson v. SmithKline Beecham Corp., 413 F.3d 1318, 1323 (Fed. Cir. 2005) (citing In re Cortright, 165 F.3d 1353, 1356 (Fed. Cir. 1999)). As a result, "an applicant's failure to disclose how to use an invention may support a rejection under . . . section 112 . . . when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention." Id. (internal quotations omitted). Conversely, "a specification disclosure which contains a teaching of the manner and

process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of [section] 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." Id. The challenging party bears the burden of showing by clear and convincing evidence that the specification lacks adequate enablement. ALZA Corp. v. Andrx Pharms., 603 F.3d 935, 940 (Fed. Cir. 2010).

D. Obviousness

Under 35 U.S.C. § 103, a "patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." "Obviousness is a question of law, which depends on several underlying factual inquiries." See Senju Pharm. Co. v. Apotex Inc., 717 F. Supp.2d 404, 418 (D. Del. 2010), aff'd, 485 Fed. App'x 433 (Fed. Cir. 2012). Those inquiries include the scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966)). We also consider as part of the obviousness analysis "secondary considerations," including commercial success, long felt but unsolved needs, and failure of others. Id. "A nonmovant may rebut a prima facie showing of obviousness with objective indicia of nonobviousness." Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1311 (Fed. Cir. 2006). "Although secondary considerations must be taken into account, they do not

necessarily control the obviousness conclusion." In re Huai–Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 418; see also Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1360 (Fed. Cir. 2011). Instead, proof of obviousness requires proof that a person of ordinary skill in the art ("POSA") "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so." Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009). A POSA would interpret prior art references "using common sense and appropriate perspective." Unigene Labs., 655 F.3d at 1361. The party challenging the validity of the patent must prove obviousness by clear and convincing evidence. See Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd., 719 F.3d 1346, 1352 (Fed. Cir. 2013)

III. Infringement and Related § 112 Challenges to the '285 Patent

The only infringement question at trial was whether DRL's ANDA II Product infringes claims 1, 2, 3, and 4 of the '285 patent. See Section I, supra. Horizon submitted evidence that DRL's ANDA II Product satisfies each limitation of the asserted claims. In response, Defendants offer a pair of arguments in the alternative. One argument (and, per Defendants, the "better decision" for us to reach) is that the asserted '285 patent claims are invalid for lack of written description on two distinct grounds. The other is that DRL's ANDA II Product cannot infringe the '285 patent if we construe the claims such that they

survive the written description challenges. In this section, we reject both written description challenges and conclude that DRL's ANDA II Product infringes the '285 patent.

A. Written Description (Uncoated Naproxen)

Defendants' first written description challenge involves two primary contentions. First, Defendants contend that claim 1 of the '285 patent encompasses formulations that include naproxen that is released immediately. Second, they contend that the '285 patent specification discloses a coordinated release product that does not permit the immediate release of naproxen. This purported disconnect between the scope of the claims and the specification forms the basis of the written description challenge. This section consequently proceeds in two parts. First, we review the parties' evidence and arguments related to the scope of the '285 patent claims and the written description of the invention in the '285 patent specification. Second, we assess whether the '285 patent claims are adequately described by the patent specification under the applicable legal standards.

1. Parties' Evidence and Arguments

(i) *Scope of the '285 patent claims*

Claim 1 of the '285 patent reads:

> A pharmaceutical composition in unit dosage form comprising therapeutically effective amounts of:
>
> (a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating; and
>
> (b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher;
>
> wherein said unit dosage form provides for release of said esomeprazole such that upon introduction of said unit dosage form

> into a medium, at least a portion of said esomeprazole is released regardless of the pH of the medium.

('285 patent at col. 22, lines 8–14.)

Any product alleged to infringe claim 1 must, of course, satisfy the enteric coated naproxen claim limitation set forth in subsection (b). The question before us is the scope of claim 1 as it pertains to ***uncoated*** naproxen that may be released into the body immediately regardless of pH level.[7] The plain language of claim 1 does not explicitly restrict the amount of uncoated naproxen that may be present in the claimed formulation and indeed the parties agree that the claim encompasses formulations that have ***at least some*** uncoated naproxen. The real dispute between the parties is whether claim 1 limits how much uncoated naproxen may be present in the claimed formulation. Broadly, Defendants urge us to adopt the "plain meaning" of the claim, which "imposes no limitation on the amount of naproxen that may be outside the enteric coating." (Dkt. 489-2 at 12.) Horizon argues that the claim covers formulations that contain uncoated naproxen so long as it is less than a "therapeutically effective amount."[8] (Dkt. 489-3 at 16–17.)

Defendants' proposed reading of claim 1 is straightforward: the plain language of the claim imposes no limitation on the amount of uncoated naproxen that may be present in claimed formulations, and it would be improper to read in such a limitation. (Dkt. 489-2 at

[7] We follow the parties in using the phrase "enteric coating" as shorthand to describe the pH-sensitive coating used to satisfy the limitation in claim 1, subsection (b). We use the term "uncoated naproxen" to mean naproxen without an enteric coating that may be released immediately regardless of pH. Because the enteric coating in Vimovo is applied around a naproxen "core" of the tablet, the term "uncoated naproxen" can also refer to the naproxen outside the (enteric coated) core.

[8] The parties appear to use the term "therapeutic amount" and "therapeutically effective amount" interchangeably.

12–14.) Defendants argue that a POSA "would recognize that any amount of naproxen outside the enteric coating (and that could fit in a "unit dosage form") would be covered by the '285 patent claims." (Id. at 12.) They note that Horizon expert Dr. Williams testified that a POSA would understand the term "comprising" to permit the inclusion of additional elements. (Id.; Tr. 821:6-25.) Dr. Williams also explained, in his infringement analysis, that he could "ignore" uncoated naproxen given the "comprising" language. (Tr. 855:12-24.)

Defendants submit that their interpretation is consistent with the history of the '285 patent because Horizon deliberately removed the claim limitation related to uncoated naproxen. (Dkt. 489-2 at 8–9.) As Defendants explain, the '285 patent differs somewhat from the earlier-issued '907 patent. Claim 1 of the '907 patent restricts the amount of uncoated naproxen that may be present by requiring NSAID surrounded by a coating that prevents the release of "essentially any NSAID . . . unless the pH of the surrounding medium is 3.5 or higher." ('907 patent at col. 20, lines 8–32.) Allegedly to avoid infringement of the '907 patent, DRL formulated its ANDA II Product with some naproxen ***outside*** of the enteric coated core of the tablet. (Dkt. 489-2 at 7.) As part of this litigation, we previously construed the term "essentially any NSAID" to mean "the minimum amount of NSAID released by an enteric coated dosage form, or tablet." (Dkt. 380 at 18–22.) Because DRL's ANDA II product redacted, we concluded that DRL's ANDA II Product does not infringe the '907 patent. (Id. at 22–23.) Horizon was later granted the '285 patent, which does not contain the "essentially any NSAID" language that formed the basis of our non-infringement finding for the '907 patent.

Horizon disagrees with Defendants' proposed reading of claim 1 of the '285 patent, and urges us to interpret the claim to limit the amount of permissible uncoated naproxen to less than a "therapeutic amount."[9] Dr. Williams testified that a POSA would understand the claim to allow only "less than a therapeutic amount" of uncoated naproxen. (Tr. 821:15–822:7.) Horizon also points to a decision from the Patent Trial and Appeal Board ("PTAB") denying Inter Partes review of the '285 patent and purportedly supporting Horizon's "therapeutic amount" limitation.[10] The PTAB concluded that claim 1 of the '285 patent "does not exclude the presence of additional naproxen outside of the coating" and "does not exclude a unit dosage form that has an amount of naproxen outside the coating that is not therapeutically effective." (PTX-351 at 13.) Consequently, the PTAB rejected the argument that claim 1 "encompass[ed] a composition where the vast majority of the naproxen, i.e., a therapeutically effective amount, would be *outside* the coating." (PTX-351 at 12.)

Defendants argue that Horizon's proposed therapeutic amount limitation is inconsistent with an FDA Citizen's Petition filed by Horizon. (Dkt. 489-2 at 26–27; DTX-1248.) In that petition, Horizon argued to the FDA that "locating ***any naproxen***

[9] The '285 patent states that the "most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in an amount between 200 mg and 600 mg." ('285 patent at col. 4, lines 11–14.) The parties accordingly appear to agree that the smallest "therapeutic amount" of Naproxen would be 50 mg. The distinction is irrelevant for infringement purposes in this case because DRL's ANDA II Product redacted.

[10] See Dr. Reddy's Laboratories, Inc. v. Pozen Inc., IPR2015-00802, Paper No. 28 (P.T.A.B. Oct. 9, 2015). For ease of reference, we will cite this PTAB decision by its trial exhibit number, PTX-351. We acknowledge Defendant Mylan's concern that it was not a party to the PTAB proceeding. (Tr. 547:23–459:19.) None of our conclusions depend on the PTAB's decision but, as discussed below, we are mindful of instances where the PTAB rejected arguments comparable to those made at trial.

outside the enteric coated core will result in the immediate release of at least some portion of the naproxen at the same time as esomeprazole is released. ***Any portion*** of the generic product's naproxen that is released prematurely in the stomach will act both topically and systemically without the benefit of the raised gastric pH produced by the esomeprazole component." (DTX-1248 at 7 (emphasis added).) In the same petition, Horizon argued that esomeprazole/naproxen combination tablets with uncoated naproxen "could subject patients to significantly increased risk of potentially fatal side effects." (DTX-1248 at 7; Tr. 436:19–437:5.) Because Horizon has separately argued to the FDA that any amount of uncoated naproxen might pose a safety risk, Defendants claim that Horizon's therapeutic amount limitation is not credible. Defendants further argue that a therapeutic amount limitation does not make sense because the FDA rejected the notion that the sequential release of esomeprazole and naproxen in Vimovo is clinically significant. (DTX-1250 at 7; Tr. 358:11-23; Tr. 462:10-23.)

Defendants also ask us to reject Horizon's proposed therapeutic amount limitation because it was not raised during discovery. (Dkt. 489-2 at 18.) Dr. Williams did not explicitly propose a therapeutic amount limitation in his deposition. Instead, Dr. Williams testified at his deposition that some amount of naproxen outside of an enteric coating might pose a safety issue but did not quantify how much. (Tr. 855:19–858:11.) Moreover, Defendants claim that Horizon "admitted" that the "plain meaning of the '285 patent claims applied and they had no limitation on the amount of naproxen that could be outside of an enteric coating." (Id. at 15.) They point to statements in Horizon's

invalidity contentions that "the disclosed dosage forms [in the '285 patent] may include additional naproxen outside the coating." (DTX-1333 at 48–49.)

Horizon in turn rejects the relevance of its Citizen's Petition to understanding the scope of the '285 patent claims. They argue that the relevant time period for our analysis is the priority date, and that any statements made in the Citizen's Petition (which was submitted years later) should not bear on our analysis. (Dkt. 489-3 at 25.) Horizon also notes that its Citizen's Petition merely "requested that the FDA require testing to ensure that products containing non-enteric coated naproxen were as safe as those that contained only enteric coated naproxen." (Id.; DTX-1248 at 2.)

(ii) *Invention as described*

Defendants submit that the '285 patent specification discloses a "coordinated release" product that does not immediately release any NSAID (*e.g.*, naproxen). The first part of Defendants' argument—that the '285 patent specification discloses a coordinated release product—is not particularly controversial. The title of the '285 patent is "Pharmaceutical Compositions for the Coordinated Delivery of NSAIDS" and the patent itself notes that the invention is directed to "pharmaceutical compositions that provide for the coordinated release of an acid inhibitor and an [NSAID] . . . ." ('285 patent at col. 1 lines 20–23.) As explained by defense expert Dr. Kibbe, "coordinated release" is the mechanism by which a formulation achieves "coordinated delivery." (Tr. 420:11–422:12.)

Evidence from both sides also indicates that coordinated release refers here to sequential delivery. The '285 patent itself discloses "the coordinated release of therapeutic agents, *i.e.*, for the sequential release of acid inhibitor followed by analgesic." ('285 patent at

col. 6, lines 23–35.) Dr. Kibbe and Horizon expert Dr. Williams both described coordinated release as sequential release. (Tr. 420:20–421:7; Tr. 861:9-12.) The description of the invention offered by the named inventor, Dr. Plachetka, also supports this view. Dr. Plachetka explained that the coordinated delivery is the immediate release of the proton pump inhibitor followed by the release of the NSAID when the pH rises to a certain level. (Tr. 43:22–44:10.) According to Dr. Plachetka, "[t]he whole point of the idea here is to get acid inhibition before the administration of the NSAID . . . ." (Tr. 134:4-5.)

The parties disagree on Defendants' second contention—namely, that the '285 patent specification does not describe formulations where some naproxen is released immediately. Dr. Kibbe testified that there were no teachings in the '285 patent specification related to formulations where naproxen is released before esomeprazole. (Tr. 431:19–432:5.) He also said that "[t]here is no support for any release of naproxen until the enteric coat comes off." (Tr. 437:11-17.) In Dr. Kibbe's view, a product that releases even some naproxen early cannot have a coordinated release within the meaning of the patent specification. (Tr. 422:14–423:16.)

Defendants point to our previous statements regarding the '907 patent specification as evidence of the nature of the invention disclosed in the '285 patent specification. Both Dr. Kibbe and Dr. Williams noted that the specifications of the two patents are essentially the same. (Tr. 419:9-22; Tr. 856:14-17.) We did observe earlier in this litigation discussing the '907 patent:

> The '907 patent's distinction from prior art is the "coordinated drug release . . . [and reduction of] intragastric acid levels to a non-toxic level prior to the release of NSAID." The specification does not contemplate an embodiment that releases a small amount of

> NSAID before the GI tract reaches a pH of 3.5 or above, nor does the specification state that releasing a small amount of NSAID would be "acceptable or part of the invention."

(Dkt. 380 at 19) (internal citations omitted).[11]

Defendants also point to Horizon's FDA Citizen's Petition as evidence that the invention disclosed in the '285 patent does not extend to formulations that immediately release some naproxen. In that petition, Horizon told the FDA that a formulation with some uncoated naproxen (*i.e.*, DRL's ANDA II Product) "obviates VIMOVO's careful design and allows release of a measureable amount of naproxen before the gastroprotective benefits of esomeprazole can take effect" and "that VIMOVO's design is intended to produce a sequential delivery of gastroprotective esomeprazole before systemic (or local) exposure to naproxen." (DTX-1248 at 2, 5.) In Defendants' view, these statements are evidence that Horizon viewed any early release of naproxen as antithetical to the key aspect of the invention—that is, delaying the release of naproxen until after the esomeprazole can take effect. (Dkt. 489-2 at 25–26.) In sum, Defendants argue that coordinated release is the "central feature" of the invention disclosed in the specification and that formulations with uncoated naproxen are "not the invention and even . . . contrary to it." (Dkt. 489-2 at 19.)

To illustrate how the '285 patent claims encompass formulations that do not have a coordinated release, Defendants offered an example of a hypothetical product containing a 50 mg naproxen core surrounded by an enteric coating, an esomeprazole

[11] Horizon disagrees that our previous statements on the '907 patent are useful in characterizing the invention and notes that the statements were made in the context of construing "essentially any NSAID," a claim term that does not appear in the '285 patent. (Dkt. 489-3 at 23–24.)

layer immediately above, and an outer layer with 49 mg of naproxen. Defendants submit that this product cannot be considered to have a "coordinated release" because nearly half of the naproxen is released immediately. (Dkt. 489-2 at 23.) They argue that such a formulation is fundamentally at odds with what Dr. Plachetka says he invented. (Tr. 134:4-5.)

Dr. Williams disagreed with Defendants and testified that a formulation with some uncoated naproxen would still have a coordinated release. (Tr. 884:4-12.) Horizon likewise rejects Defendants' use of a hypothetical formulation, which, in their view, "in no way represent[s] any of Defendants' ANDA products" and for which there is no evidence "that a person of skill in the art exercising any sort of reason would actually contemplate making or using them." (Dkt. 489-3 at 15.) Horizon argues that "even if Defendants' unrealistic, hypothetical embodiments fell within the literal scope of the claims, one of skill in the art would understand them to be unreasonable and inoperable embodiments and would not pursue them." (Id.)

2. Analysis

We turn now to the question of whether the '285 patent claims are adequately described by the '285 patent specification. As summarized above, the parties dispute both the scope of the claimed invention and the adequacy of the written description. As to the scope of the claims, we agree with Defendants that claim 1 of the '285 patent—whose only naproxen-related limitation relates to enteric coated naproxen—does not limit the amount of

uncoated naproxen that may be present in claimed formulations.[12] It is well understood in patent law that the term "comprising" does not exclude additional elements in addition to the elements named in the claim. See Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1344–45 (Fed. Cir. 2003) ("Comprising is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."). The language of the claim itself does not preclude uncoated naproxen. We are not persuaded by Horizon's argument that we should read in a "therapeutic amount" limitation on uncoated naproxen, particularly as that interpretation finds little support in the claim language, specification, or anywhere else. See Omega Eng'g, Inc, v. Raytek Corp., 334 F.3d 1314, 1323 (Fed. Cir. 2003) (noting "heavy presumption that claim terms carry their full ordinary and customary meaning" (internal quotations omitted)).

We disagree with Defendants, however, that the '285 patent specification precludes the inclusion of uncoated naproxen in the formulations it describes. The specification itself is silent on whether the formulation can include uncoated naproxen ***in addition to*** the enteric coated naproxen present in the claimed formulation. Defendants point out, fairly, that the '285 patent specification describes a product whose embodiments "preferably" provide for coordinated drug release such that "the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract is risen." ('285 patent at col. 4, lines 45–51.) It is likewise true that the specification explains that the invention is at

[12] Any such uncoated naproxen would necessarily be in addition to the therapeutic amount of enteric coated naproxen required by subsection (b) of claim 1.

least in part directed toward resolving injuries associated with NSAIDs being released "before the pH of the gastrointestinal tract can be raised . . . ." (Id. at col. 1, lines 60–64.) We agree that these and other statements in the specification might counsel a POSA against incorporating uncoated naproxen when formulating the described invention. Indeed, Horizon expert Dr. Williams expressed skepticism about a hypothetical formulation that contained uncoated naproxen because he did not "know why someone would want to do this" when the patent was "about preventing the release of . . . of the therapeutic amount of NSAID from that enteric coating until the pH is above 3.5." (Tr. 883:12-24.)

That the specification can be read to convey a preference for formulations without uncoated naproxen, however, does not warrant invalidating the claims under § 112(a). To hold otherwise would be to invalidate the claims simply because they encompass less preferable embodiments—a reading of § 112(a) that we find incompatible with patent law principles. See, e.g., Cordis Corp. v. Medtronic AVE, Inc., 339 F.3d 1352, 1365 (Fed. Cir. 2003) ("an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention"); Gillette Co. v. Energizer Holdings, Inc., 405 F.3d 1367, 1371 (Fed. Cir. 2005) ("a patentee typically claims broadly enough to cover less preferred embodiments as well as more preferred embodiments, precisely to block competitors from marketing less than optimal versions of the claimed invention"); Golight, Inc. v. Wal-Mart Stores, Inc., 355 F.3d 1327, 1331–32 (Fed. Cir. 2004) ("An applicant is not necessarily required by 35 U.S.C. § 112 . . . to describe more

embodiments than its preferred one, and . . . [it has] outright rejected the notion that disclosure of a single embodiment necessarily limits the claims.")

We note that Defendants have offered an unusual written description challenge here that appears to have little support in the law. Rather than allege that a specific element of the claim lacks support in the specification, Defendants argue that the claim is invalid for merely ***allowing the possibility*** of the addition of uncoated naproxen in view of the specification. The question of whether a POSA would view the '285 patent specification (and Defendants' other extrinsic evidence) as limiting the plain language of the claim to preclude the presence of uncoated naproxen would seem a more natural fit for claim construction proceedings. The law of written description requires us to evaluate whether the four corners of the specification "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Ariad, 598 F.3d at 1351–52. Our inquiry is therefore whether the '285 patent specification would reasonably convey to a POSA that Dr. Plachetka had possession of the "invention"—here a combination drug product featuring enteric coated naproxen and an uncoated proton pump inhibitor ("PPI"). As Dr. Williams explained at trial, those elements are indeed present and described in the specification. (Tr. 812:17–824:10.) Whether there is extrinsic evidence, such as Horizon's FDA Citizen's petition, suggesting that the presence of uncoated naproxen was against the spirit of the invention does not bear on our written description analysis. Because Defendants have not demonstrated by clear and convincing evidence that any element of the claimed invention lacks written description support, we decline to invalidate the '285 patent on those grounds.

B. Written Description (Sustained Release Formulations)

Defendants' second written description challenge arises out of the use of the term "inhibits" in claim 1 of the '285 patent. In their view, the use of the word "inhibits" extends the scope of the claim to include "sustained release" formulations while the specification discloses only "delayed release" formulations. As above, we first review the parties' evidence and arguments related to the scope of the claims and the description in the patent specification. We then analyze whether the claims satisfy the written description requirement of § 112(a) on this issue.

1. Parties' Evidence and Arguments

(i) *Scope of the '285 patent claims*

Claim 1 of the '285 patent requires, *inter alia*, "naproxen surrounded by a coating that ***inhibits its release*** from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher." ('285 patent claim at col. 22, lines 12–14 (emphasis added).) Defendants submit that the term "inhibits" should be given its plain meaning, "to slow down." (Dkt. 489-2 at 12; Tr. 887:1-7.) They highlight a previous filing in this case where Horizon agreed that the plain meaning of "inhibit" was "slow down or stop" and that "inhibit" in the '285 patent claims takes on this plain meaning. (DTX 1333 at 51.)

Defendants also contend that the term "inhibits" should be understood to be broader than the term "prevents" because the term was consciously selected by the inventor to expand the scope of the '285 patent claims beyond what was claimed in the '907 patent. (Dkt. 489-2 at 30.) Claim 1 of the earlier-issued '907 patent requires an "NSAID . . . surrounded by a coating that . . . ***prevents the release*** of essentially any NSAID from said

dosage form unless the pH of the surrounding medium is 3.5 or higher." ('907 patent at col. 20, lines 22–27 (emphasis added).) Horizon expert Dr. Williams agreed that a POSA might presume that "inhibits" in the '285 patent means something different than "prevents" in the '907 patent because the language is different in the two claims. (Tr. 892:20-24; see also Tr. 885:8-17.) Per defense expert Dr. Kibbe, the term "inhibits" (understood as "slows down") extends the scope of the claim to "sustained release" formulations. (Tr. 416:4-23; 438:12–441:14.) A sustained release product, as described by Dr. Kibbe, is one that "begins releasing right away, but it does so at a slower rate than you would see if you were comparing it to an immediate-release product." (Tr. 441:10-13.) Dr. Kibbe contrasted sustained release products, which allow for immediate (albeit slowed) release of the active ingredient, with formulations that "stop" drug release, meaning that "for a fixed period of time, no drug will come out until the dosage form migrates into an area where the pH is above the pH of the enteric coat." (Tr. 441:6-9.)

Horizon argues that a POSA "would recognize that the term 'inhibit' in the '285 patent describes the same goal as the term 'prevent' in the context of the '907 patent." (Dkt. 489-3 at 27.) As Dr. Williams testified, "inhibit" would be understood by a POSA "to accomplish the goal of no release in the stomach, in acid, or until the pH is 3.5 or higher." (Tr. 814:21–815:2.) That understanding, according to Horizon, would arise out of a POSA's reading of the specification (discussed below). Horizon also urges us to reject Dr. Kibbe's trial testimony as incredible in light of previous statements in his expert

report that "[a] person of ordinary skill in the art would understand the word 'inhibit' to mean 'prevent' based upon the specification of the '285 patent." (Tr. 556:7-12.)

(ii) *Invention as described*

Defendants submit that the '285 patent specification does not contain any disclosure related to "sustained release" products—*i.e.*, formulations that slowly but immediately release the active ingredient. Instead, Dr. Kibbe pointed to various instances in the '285 patent specification that refer specifically to "prevent[ing]" the release of naproxen. (Tr. 439:14–440:17; see, e.g., '285 patent at col. 4, lines 64–67; id. at col. 5, lines 34–39; id. at col. 9, lines 30–33.) As he explained, the term "inhibits" is not used in the specification to refer to the release of naproxen; to the extent it is used at all, it describes proton pump inhibition. (Tr. 438:15–439:2.) Horizon expert Dr. Williams agreed that the specification does not "talk[] about" sustained release formulations. (Tr. 890:19-24.)

Horizon submits that the specification does disclose what it means to "inhibit" in the context of a coating. (Dkt. 489-3 at 27; Tr. 814:18-20.) The '285 patent describes two types of coatings that may be used to surround the NSAID. (Dkt. 489-3 at 28.) One is the pH-sensitive enteric coating that does not dissolve until the pH of the surrounding medium is 3.5 or higher. (See, e.g., '285 patent at col. 4, lines 54–59.) The other coating described "controls the release of NSAID by time, as opposed to pH, with the rate adjusted so that NSAID is not released until after the pH of the gastrointestinal tract has risen to at least 3.5." (Id. at col. 4, lines 59–67.) In Horizon's view, these alternatives

describe coatings that either ***prevent*** the release of naproxen at low pH or ***delay*** its release until sufficient time has passed to allow the pH to rise. (Dkt. 489-3 at 28.)

2. Analysis

Defendants argue that claim 1 of the '285 patent fails the written description requirement of 35 U.S.C. § 112(a) because the claim encompasses sustained release formulations and the patent specification does not describe sustained release formulations. (Dkt. 489-2 at 29–30.) Their argument primarily rests on the assertion by defense expert Dr. Kibbe that the use of the term "inhibits" in claim 1 broadens the claim to encompass "sustained release" formulations. (Tr. 438:15–439:2.)[13]

We note that the PTAB recently rejected a similar argument from DRL. In that proceeding, as here, the parties argued over whether "inhibits" should be afforded its ordinary meaning or interpreted to mean something akin to "prevents." (PTX-351 at 13.) DRL argued then that claim 1 of the '285 patent "encompass[es] formulations that release all of its naproxen slowly at any pH, instead of preventing release until the formulations are in a medium with a pH of 3.5 or higher." (Id. at 14.) The PTAB declined to provide an explicit definition of "inhibits" because it did not "discern a significant difference between the definitions offered by the parties." (Id.) The PTAB, however, "disagree[d] with [DRL]'s interpretation of the difference in breadth between 'inhibit,' 'prevent,' and 'delay,' [which] would lead to the conclusion that the claims of the '285 patent encompass a formulation that releases all of its naproxen slowly at any pH." (Id. at 14–

[13] As with Defendants' written description challenge in Section III.A, supra, the question of whether use of the claim term "inhibits" broadens the scope of the claim appears more properly considered a claim construction issue than a written description challenge.

15.) Accordingly, the PTAB concluded that the claims of the '285 patent, including the term "inhibits," were adequately supported by the relevant specification. (Id. at 19.)

We conclude that Defendants have failed to meet their burden to show by clear and convincing evidence that claim 1 of the '285 patent lacks written description support. We are not convinced that use of the term "inhibits" in claim 1 expands the scope of the claim to include sustained release formulations. A POSA reading the specification would understand that the term "inhibits" in the context of the patent refers back to the enteric coatings described in the patent specification that encompass both preventing and delaying the release of naproxen. (See, e.g., '285 patent at col. 4, lines 54–67.) Put another way, given the description in the specification of coatings that "inhibit" the release of an NSAID in specific ways, (Tr. 815:6–9), we are unconvinced that a POSA would understand that claim 1 of the '285 patent encompasses sustained release formulations. Because we conclude that the claim does not encompass sustained release formulations, we need not reach the question of whether the specification adequately describes such formulations.

C. Infringement

Horizon alleges that DRL's ANDA II Product infringes claims 1– 4 of the '285 patent. Having evaluated the scope and meaning of the pertinent claim terms above, we now compare those claims against the allegedly infringing product. Advanced Steel Recovery, LLC v. X-Body Equip., Inc., 808 F.3d 1313, 1316 (Fed. Cir. 2015). DRL's ANDA II Product [redacted] (PTX-234 at 25.) DRL's "500

mg/20 mg" dose ANDA II Product [redacted]. (Id.) DRL's "375 mg/20 mg" dose ANDA II Product [redacted]. (Id.) [redacted]. (Id.) In addition, [redacted] (PTX-014 at 15.) We now turn to whether the product satisfies the various claim limitations of the asserted claims.[14]

1. Claim 1 of the '285 patent

(i) *"a pharmaceutical composition in unit dosage form"*

Horizon provided unrebutted testimony that the DRL ANDA II Product is "a pharmaceutical composition in unit dosage form." (Tr. 833:18-834:1.)

(ii) *"therapeutically effective amounts of: (a) esomeprazole, wherein at least a portion of said esomeprazole is not surrounded by an enteric coating"*

Horizon provided unrebutted testimony that the DRL ANDA II Product includes a "therapeutically effective amount[] of esomeprazole." (Tr. 834:5–835:5.) Further, the esomeprazole in the DRL ANDA II Products is not surrounded by an enteric coating. (Tr. 835:6-20; PTX-234 at 25.)

(iii) *"therapeutically effective amounts of: (b) naproxen surrounded by a coating that inhibits its release from said unit dosage form unless said dosage form is in a medium with a pH of 3.5 or higher"*

Horizon provided unrebutted testimony that the DRL ANDA II Product [redacted], both of which are therapeutically

[14] Mylan takes no position on whether DRL's ANDA II Product infringes the '285 patent. (Dkt. 489-2 at 6.)

effective amounts. (Tr. 835:22–836:12.) redacted DRL II ANDA Products redacted redacted. (Tr. 838:8-21.)

(iv) *"wherein said unit dosage form provides for release of said esomeprazole such that upon introduction of said unit dosage form into a medium, at least a portion of said esomeprazole is released regardless of the pH of the medium"*

Horizon provided unrebutted testimony that DRL's ANDA II Product redacted

(Tr. 838:22–839:15.)

Because DRL's ANDA II Product satisfies each limitation of claim 1 of the '285 patent, we find that Horizon has proven by a preponderance of the evidence that DRL's ANDA II Product infringes that claim.

2. Claim 2 of the '285 patent

Claim 2 of the '285 patent reads: "The pharmaceutical composition of claim 1, wherein naproxen is present in said unit dosage form in an amount of 200-600 mg." ('285 patent at col. 22, lines 19–21.) Horizon provided unrebutted testimony that DRL's ANDA II Product redacted (Tr. 840:1-8.)

Because DRL's ANDA II Product satisfies each limitation of claim 2 of the '285 patent, we find that Horizon has proven by a preponderance of the evidence that DRL's ANDA II Product infringes that claim.

3. Claim 3 of the ’285 patent

Claim 3 of the ’285 patent reads: “The pharmaceutical composition of claim 1, wherein esomeprazole is present in said unit dosage form in an amount of from 5 to 100 mg.” (’285 patent at col. 22, lines 22–24.) Horizon provided unrebutted testimony that DRL’s ANDA II Product redacted (Tr. 840:9-15.)

Because DRL’s ANDA II Product satisfies each limitation of claim 3 of the ’285 patent, we find that Horizon has proven by a preponderance of the evidence that DRL’s ANDA II Product infringes that claim.

4. Claim 4 of the ’285 patent

Claim 4 of the ’285 patent reads: “The pharmaceutical composition of claim 1, wherein naproxen is present in said unit dosage form in an amount of between 200-600 mg and esomeprazole in an amount of from 5 to100 mg per unit dosage form.” (’285 patent at col. 22, lines 25–29.) Horizon provided unrebutted testimony that the naproxen in DRL’s ANDA Product redacted (Tr. 840:1-8.) redacted DRL’s ANDA II Products redacted (Tr. 840:9-15.)

Because DRL’s ANDA II Product satisfies each limitation of claim 4 of the ’285 patent, we find that Horizon has proven by a preponderance of the evidence that DRL’s ANDA II Product infringes that claim.

IV. Obviousness and Related § 112 Challenges

Defendants at trial offered a second line of interrelated invalidity challenges under 35 U.S.C. § 103 and § 112. These issued were briefed separately from the infringement and § 112 issues argued in Section III, supra, and are consequently considered together in this section. Section IV.A addresses the Defendants' obviousness challenge under § 103. Sections IV.B and IV.C address the Defendants' related enablement and written description challenges under § 112.

A. Obviousness

We undertake several factual inquiries to determine whether the Asserted Patents are invalid under § 103, including determining the scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007). In this section, we recount the parties' evidence at trial pertaining to the prior art as well as so-called secondary considerations of nonobviousness. We then assess that evidence and ultimately conclude that the Defendants have failed to meet their burden to show that the Asserted Patents are invalid under § 103.

1. Parties' Evidence and Arguments on Prior Art

Defendants maintain that a POSA would have been "motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so." Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009). They submit two theories as to why the invention disclosed in the Asserted Patents (the "Invention") was obvious under the prior

art.[15] (Dkt. 489 at 15–27.) Those theories primarily involve prior art pertaining to existing combination drug products and other art describing NSAID/PPI co-therapies, and are discussed in Section IV.A.1.i, infra. Horizon's primary defense is that the invention cannot be considered obvious because the invention uses an "uncoated" PPI. The parties' extensive dispute over the prior art as it relates to uncoated PPIs is discussed in Section IV.A.1.ii, infra.

(i) *Defendants' obviousness theories*

Defendants offer two theories of why the Invention was obvious under the prior art. The first theory is that it would have been obvious to a POSA to improve upon the combination product described in U.S. Patent No. 5,601,843 (the '843 patent) (DTX-1063) and commercialized as Arthrotec. (Dkt. 489 at 25.)[16] Arthrotec is a branded drug product that combines an NSAID (diclofenac) with misoprostol (a synthetic prostaglandin). (DTX-1095 at 2.) Arthrotec is used to treat conditions such as osteoarthritis and rheumatoid arthritis in patients with a high risk of developing NSAID-related injuries such as gastric and duodenal ulcers. (Tr. 322:15-20.) The misoprostol in Arthrotec was designed to reduce the risk of NSAID-related injury by: (1) replacing prostaglandin in the stomach to protect the stomach from acid exposure; (2) inhibiting

[15] We undertake our obviousness analysis from the perspective of a POSA as of June 1, 2001, the date on which Provisional application No. 60/294,588 was submitted. Horizon expert Dr. Williams stated at trial that he used a priority date of May 31, 2002 but later agreed to use the earlier 2001 priority date. (Tr. 729:8–731:8; dkt. 489 at 18.)

[16] Horizon argues that some of Defendants' arguments at trial constituted new (and therefore impermissible) combinations of prior art. (Dkt. 489-1 at 23–24.) Because we conclude that the Invention was nonobvious under Defendants' proffered combinations, we do not reach the question of whether Defendants waived particular combinations during discovery.

acid production in the stomach. (Tr. 456:10–15; Tr. 495:4–9; Tr. 501:18–21.) Of these mechanisms, the prostaglandin replacement mechanism was the "primary" mechanism by which misoprostol would help reduce the risk of NSAID-related injury. (Tr. 502:16–503:10.) In Defendants' telling, the only significant difference between Arthrotec and the Invention is the choice of "acid inhibitor" (a PPI instead of misoprostol) and NSAID (naproxen instead of diclofenac). (Tr. 456:23–457:17; Tr. 461:12-24.)

Defendants submit that the Invention was obvious because a POSA would have been motivated to replace the misoprostol in Arthrotec with a PPI, and particularly esomeprazole. They argue that a POSA would have replaced misoprostol with esomeprazole because: (1) misoprostol was understood to have harmful side effects; and (2) misoprostol was understood to be less effective than esomeprazole for treating NSAID-related injuries. As to the first point, experts from both sides testified that misoprostol carried significant side effects, including diarrhea, flatulence, and even spontaneous abortion. (Tr. 311:7-10, Tr. 330:12-23; Tr. 463:17-23; Tr. 1180:11–1182:14; DTX-1095 at 2.) These side effects were well documented in the prior art. ('907 patent at col. 2, lines 52–56.) As to the second point, Defendants submit that it was understood in the prior art that PPIs, and especially esomeprazole, were superior to other acid inhibitors, including misoprostol, for treating NSAID-related injuries. (Tr. 309:11–317:9; Tr. 464:4-10.)

Defendants highlight academic literature indicating that PPIs were understood to be a better treatment option for NSAID-related injuries than other available acid inhibitors such as H2-receptor antagonists and prostaglandins. Much of the literature

relies on two studies comparing PPIs with alternative treatments. The Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (or "OMNIUM") study compared the PPI omeprazole to misoprostol. (DTX-1077; Tr. 312:19-25.) The Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer treatment (or "ASTRONAUT") study compared omeprazole with the H2-receptor antagonist ranitidine. (DTX-1069.)

Subsequent articles reviewing the safety and efficacy of treatments for NSAID-related injuries cite the OMNIUM and ASTRONAUT studies. As recounted in Brown (DTX-1080), the OMNIUM study reported that use of omeprazole resulted in a reduction in the reoccurrence of NSAID-related ulcers and increased compliance compared with misoprostol. (DTX-1080 at 7; Tr. 316:5-25; Tr. 1207:3–1209:12.) Per Brown, "[PPIs] have demonstrated efficacy in the prevention of the adverse gastrointestinal effects of NSAIDs" and have "clear benefits" over alternatives. (DTX-1080 at 8.) Another article, Wolfe (DTX-1089), explained that the "more potent inhibition of gastric acid secretion provided by PPIs enhances their healing properties." (DTX 1089 at 10; Tr. 310:20–311:10.) Citing the ASTRONAUT study comparing omeprazole with H2-agonist ranitidine, Wolfe and Brown both recommended the use of PPIs over H-2 antagonists. (Tr. 316:6-11.) Relying in part on these articles, defense expert Dr. Metz testified that PPIs were understood to be the best acid inhibitor as of the priority date for both effectiveness and tolerability. (Tr. 309:22-24.) Moreover, Dr. Metz testified that a POSA would have been motivated to replace the misoprostol in Arthrotec with esomeprazole in particular because it was understood to be the most potent PPI. (Tr.

331:19–332:13; Tr. 337:13-17.) Dr. Kibbe testified that it would have been a routine modification to use a PPI instead of misoprostol in formulating the product. (Tr. 461:21–462:4.)

Defendants argue that a POSA would have had additional motivation to replace the misoprostol in Arthrotec with a PPI because NSAID/PPI combination therapies were already known in the prior art. (Tr. 332:8-13.) For example, International Patent Pub. No. WO 97/25064 ("Depui") (DTX-1064) disclosed a combination dosage form of a PPI with an NSAID for treatment and prevention of NSAID-related injury. (Tr. 325:23–327:1; Tr. 464:11–466:6.) Acceptable PPIs in Depui included omeprazole and esomeprazole, while acceptable NSAIDs included naproxen. (Tr. 326:19–327:1.) Defendants also point to U.S. Patent No. 6,544,556 (the '556 patent) (DTX-1118), which disclosed a combination dosage form of a PPI with an NSAID to prevent NSAID-related injury. ('556 patent at col. 1, lines 7–14.)[17] Specifically, the '556 patent discloses the use of a PPI combined with diclofenac (the same NSAID found in Arthrotec). (Id. at col. 4, lines 51–54; Tr. 1216:17–1219:4.) They also cite U.S. Patent No. 5,204,118 ('118 patent) (DTX-1051), which discloses combination dosage forms of an "[NSAID] or acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition." ('118 patent at col. 1, lines 13–16.)

[17] There is some dispute as to whether the '556 patent is prior art. (Dkt. 489-1 at 22 n.4.) The '556 patent issued on April 8, 2003, from a patent application filed on September 11, 2000. Accordingly, it is prior art under former 35 U.S.C. § 102(e), which includes as prior art "a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent." Our finding of nonobviousness, however, does not turn on whether the '556 patent is considered prior art.

Horizon disputes that a POSA would have been motivated to replace the misoprostol in Arthrotec with a PPI such as esomeprazole. Horizon rejects the notion that a PPI and a synthetic prostaglandin, such as misoprostol, would be seen as interchangeable because they have different mechanisms of action. Misoprostol helps replace prostaglandins, the depletion of which makes the stomach more susceptible to NSAID-related injury. (Tr. 1138:15–1139:4; PTX-292.) In contrast, PPIs act as "acid suppressants" or "acid inhibitors" that do not replace the loss of prostaglandins due to NSAID use. (Tr. 503:16–25; Tr. 1259:20–1260:4.) Dr. Plachetka, the named inventor of the Asserted Patents, similarly explained that "the only thing that a proton pump inhibitor will do is inhibit the secretion of acid . . . , whereas misoprostol will repair or replace the gel coat." (Tr. 40:4-13.) In light of these differences, Horizon argues that a POSA would not have been motivated to swap the two ingredients. (Dkt. 489-1 at 47.)

Horizon argues further that a POSA would not have been motivated to replace the misoprostol in Arthrotec with ***uncoated*** esomeprazole. Although we discuss the prior art related to uncoated PPIs in detail below, Horizon expert Dr. Williams testified that a POSA would not have chosen to replace misoprostol, which is not acid labile, with a PPI that ***is*** acid labile. (Tr. 773:22–774:5; Tr. 774:8-17.) The distinction also matters, in Horizon's view, because much of the prior art discussing the efficacy of PPIs analyzed enteric coated PPIs. The OMNIUM and ASTRONAUT studies, for example, were conducted using enteric coated PPIs. (Tr. 384:12–386:1.)

The second obviousness theory proffered by Defendants relies on essentially the same references but in a different logical progression. Whereas their first theory is that a POSA

would have been motivated to replace the ingredients in a combination drug product (*e.g.*, Arthrotec) with an NSAID/PPI combination, the second theory is that a POSA would have been motivated to take existing NSAID/PPI co-therapies and put them into a combination drug product . (Dkt. 489 at 15–27.) As discussed above, NSAID/PPI co-therapies were known in the prior art. (See, e.g., Depui (DTX-1064); '556 patent (DTX-1118); Tr. 325:23–327:1; Tr. 464:11–466:6.) At the same time, it was understood that administering medications separately "can be difficult to achieve and can be difficult for a patient to faithfully follow." (Tr. 319:17–321:19.) Requiring patients to take multiple tablets per day can lead to patients forgetting or declining to take both tablets. (Tr. 319:17–321:7; Tr. 458:7-23.) Defense expert Dr. Metz testified that a POSA would have sought to address potential compliance issues by combining drug components into a single tablet. (Tr. 321:16-19.) As an example, he highlighted the '843 (Arthrotec) patent, which disclosed that combination tablets could improve patient compliance. ('843 patent at col. 12, lines 10–14; Tr. 321:24–324:17.)[18]

Defendants explain that the prior art also disclosed combination drug therapies with "coordinated release" (*i.e.*, the sequential release of an acid inhibitor and an NSAID). U.S. Patent No. 6,319,519 ('519 patent) (DTX-1112) discloses a tablet comprised of an NSAID (to treat arthritis pain and inflammation) and misoprostol (to prevent NSAID-related injury). (Tr. 913:7-915:23; '519 patent at col. 1, lines 9–34.) According to the '519 patent, "[i]t has been found experimentally that it is necessary for

[18] Defendants also argue that the dependent claims (*e.g.*, claim 52 of the '907 patent) would be obvious because it was understood that an NSAID in conjunction with a PPI could be used to treat osteoarthritis or rheumatoid arthritis. (Tr. 88:23–89:4; Tr. 333:21–334:2; Tr. 338:10-24.)

the prostaglandin to be released before the NSAID so as to protect the stomach from the effects of the NSAID. It is therefore preferable that the NSAID is coated to delay release." ('519 patent at col. 1, lines 21–25.) Horizon expert Dr. Williams conceded at trial that the coordinated release structures described in the '519 patent and the '843 Arthrotec patent are similar to the coordinated release mechanism of the Invention. (Tr. 915:20–917:3; see also Tr. 454:2–457:17.)

(ii) *Uncoated PPIs*

Horizon's primary response to Defendants' obviousness arguments is that the Invention was nonobvious because it uses an uncoated PPI and the prior art taught away from using uncoated PPIs.[19] (Dkt. 489-1 at 27–43; 45–49.) Horizon argues that it was widely understood—and reflected in the prior art—that PPIs must be enteric coated because they are susceptible to acid degradation in the stomach. Defendants disagree that the prior art taught away from using uncoated PPIs and offered testimony at trial why a POSA would have had a reasonable expectation of success using an uncoated PPI. We summarize below the parties' evidence on these subjects.

Horizon's experts testified that a POSA would not have been motivated to use an uncoated PPI. Dr. Williams explained that, as of the priority date, all commercially available PPIs were formulated with an enteric coating. (Tr. 733:2-13; Tr. 735:8-23; see also Tr. 372:23–373:5.) He testified that PPIs were enteric coated because they are acid labile and dissolve much more quickly in acidic pH environments. (Tr. 733:16–735:1.)

[19] We use "uncoated PPI" in this section as shorthand to refer to a PPI that does not have a pH-sensitive enteric coating.

In Dr. Williams' view, this understanding was reflected in prior art that affirmatively discouraged the use of non-enteric coated PPIs. (Tr. 737:1-18.) For example, Pilbrant 1985 (PTX-325) evaluated the use of enteric coated and uncoated omeprazole solid dosage formulations, and concluded that the uncoated dosage form was "ruled out in a pilot bioavailability study . . . where it was shown that more than half of the omeprazole in a rapidly dissolving dosage form degrades in the stomach." (PTX-435 at 2; Tr. 738:16–740:1.) In contrast, Pilbrant 1985 stated that an enteric coated solid dosage form "offer[ed] the best possibilities." (PTX-435 at 3; Tr. 740:15-22.) Per Dr. Williams, a POSA would conclude from Pilbrant 1985 that a non-enteric coated PPI would not work and would be discouraged from pursuing such a formulation. (Tr. 740:2-14.) Although he did not discuss each in detail, Dr. Williams testified that 25 additional prior art references supported his contention that PPIs must be enteric coated.[20] (Tr. 747:20–748:12.)

Horizon notes that Defendants' own experts have acknowledged the need to enteric coat PPIs because of their acid lability. (Tr. 502:5-15.) Dr. Metz co-authored an article stating that "[p]roton pump inhibitors are inactivated by gastric acid and thus ***must*** be given as enteric coated granules in gelatin capsules or enteric coated tablets." (PTX-73 at 8 (emphasis added); Tr. 365:6–369:5.) Dr. Metz testified at trial that it was the

[20] See (PTX-77 at 3); (PTX-78 at 4); (PTX-79 at 3); (PTX-80 at 2); (PTX-242 at 3); (PTX-243 at 2); (PTX-244 at 2); (PTX-245 at 2); (PTX-246 at 4); (PTX-247 at 9); (PTX-248 at 5); (PTX-249 at 6); (PTX-250 at 2); (PTX-251 at 2); (PTX-252 at 2); (PTX-253 at 3); (PTX-254 at 4); (PTX-255 at 10); (PTX-256 at 2); (PTX-257 at 1); (PTX-258 at 6); (PTX-337 at 5); (PTX-570 at 4–5); (PTX-573 at 5–6); and (DTX-1117 at 13). We recognized at trial that PTX-79 cannot be considered prior art. (Tr. 528:19–529:16.)

"general party line" and belief in the industry that "proton pump inhibitors are inactivated by gastric acid and thus must be given as enteric coated granules in gelatin capsules or enteric coated tablets." (Tr. 369:11-21; Tr. 370:16-20; Tr. 371:16-21.) Dr. Mayersohn likewise testified in a sworn expert declaration in another case that "[b]ecause PPIs are chemically unstable in the acidic environment of the stomach, they must be protected from stomach acid. Drug manufacturers accomplish this by combining the PPI with various stabilizers and coatings, resulting in a drug formulation that has an outer layer (referred to as the 'enteric coat') that protects the PPI from stomach acid." (PTX-434 at 6; Tr. 686:4–689:12.) In light of the prevailing understanding about uncoated PPIs, Horizon argues that a POSA would have understood that using an uncoated PPI in a formulation would fail because of acidic gastric pH levels. (See, e.g., Tr. 737:1-18; 1029:9-22; 1163:10–1164:3.)

Defendants disagree with Horizon's characterization of the prior art, which they see as, at most, expressing a general preference for enteric coated PPIs. (Dkt. 489 at 48.) They criticize Horizon's 25 "teaching away" references that purportedly counsel against using an uncoated PPI on several grounds. Defense expert Dr. Mayersohn explained that one of Horizon's references merely states that omeprazole is acid labile and enteric coated, and does not discuss uncoated PPIs. (Tr. 613:5–614:13 (discussing PTX-256).) Dr. Mayersohn testified that some of the other references were "repetitive and duplicative," (Tr. 611:20-23) while Dr. Kibbe explained that "often the same thing is repeated and repeated in articles because it's easier to do that than to actually test it." (Tr. 527:16-19.) Defendants criticized ten of the references for being AstraZeneca

publications, who they argue had an interest in promoting "the benefits of AstraZeneca's own, patented, enteric coated PPI formulation." (Dkt. 489 at 49; Tr. 939:5–945:4.) Defendants criticized another six references as lacking original research or analysis on the efficacy or usefulness of uncoated PPIs. (Tr. 968:13–970:2.)

Defendants also submitted that a POSA would have been motivated to use uncoated PPIs and would have had a reasonable expectation of success in doing so because: (1) the PPI could be administered with an alkalizing agent to help protect it from stomach acid; (2) the dose of the PPI could be increased to offset acid degradation; (3) the repeated dosing of the PPI would create a "feedback loop" that would increase bioavailability for the uncoated PPI over time; and (4) an uncoated PPI would have certain advantages over an enteric coated PPI.

Alkalizing Agent

Defendants argue that a POSA would have a reasonable expectation of success using an uncoated PPI because the formulation could include an alkalizing agent, such as sodium bicarbonate, that would protect the PPI from degradation by stomach acid. (Dkt. 489 at 43–44.) Dr. Kibbe testified that an alkalizing agent could raise the pH of the stomach around the tablet and protect the PPI from degradation. (Tr. 485:1-16.) He explained that Pilbrant 1985 teaches that an omeprazole-sodium bicarbonate combination could be used to improve bioavailability. (Tr. 489:15-23; PTX-435 at 4–5.) Other prior art, including U.S. Patent No. 6,489,346 (the '346 patent) (DTX-1117), eventually commercialized as Zegerid, disclosed an omeprazole and sodium bicarbonate formulation. (Tr. 345:1-20; Tr. 483:11–484:10.) Although Horizon submitted the '346

patent as one of its "teaching away" references, Defendants submit that it would have taught a POSA to account for PPI's acid lability by co-administering an alkalizing agent. (Dkt. 489 at 49; Tr. 977:16–980:21.)

Horizon expert Dr. Williams disagreed that sodium bicarbonate could feasibly be added to the formulation to prevent acid degradation. He testified, citing Pilbrant 1993 (PTX-262), that the resulting tablet would be too large because of the amount of sodium bicarbonate needed. (Tr. 758:3–760:16.)[21] Dr. Williams also argued, citing International Patent Publication WO 00/026185 (DTX-1102), that sodium bicarbonate would be incompatible with the enteric coated naproxen also present in the formulation because it could dissolve that enteric coat. (Tr. 753:21–755:16.)

Increased PPI Dosage

Defendants also argue that a POSA would have a reasonable expectation of success using an uncoated PPI because a POSA could increase the dosage level to account for the PPI's acid lability. Dr. Mayersohn cited Clissold (DTX-1036) for the proposition that about 50% of an uncoated PPI remains bioavailable despite acid degradation. (Tr. 620:7–621:6; DTX-1036 at 19 (citing Pilbrant 1985).) As some of the uncoated PPI remains available to the body (or "bioavailable"), Dr. Mayersohn explained that a POSA could account for acid degradation by increasing the amount of PPI in the formulation—in this case by essentially doubling the dose to account for the PPI's 50% bioavailability. (Tr. 621:23–622:7; Tr. 704:18–705:2.) Dr. Metz likewise testified that

[21] Defendants argue that Horizon's "tablet size" arguments do not account for the possibility of multiple dosages nor mechanisms such as the "feedback loop" discussed below that might make smaller amounts of PPI effective. (Dkt. 489 at 44–45.)

the PPI dose could be doubled to account for acid degradation. (Tr. 390:2-6.) Dr. Mayersohn added that a POSA would have further reason to believe that increasing the dosage would be effective because Regårdh (DTX-1029) taught that a comparatively higher percentage of PPI would be bioavailable at higher dosage levels. (Tr. 635:23–636:22.)

Horizon rejects the idea that a POSA would have been motivated to increase the dose of PPI to account for its acid lability. First, Dr. Taft questioned whether the 50% bioavailability figure from Pilbrant 1985 (PTX-432), which explicitly related to suspensions of omeprazole, could be used as a proxy for the bioavailability of a drug in tablet form. (Tr. 1060:5–1061:10.) Dr. Williams added that a subsequent study, Pilbrant 1993 (PTX-262), indicates that as much as 84% of a PPI may be lost due to acid degradation.[22] (Tr. 778:12–780:7.) Second, even assuming a 50% bioavailability, Dr. Taft testified that a POSA would not have simply doubled the dose to address the acid lability of PPIs. (Tr. 1067:9–1068:3.) On cross-examination, Defendants' experts could not provide any examples of situations where low bioavailability was addressed through doubling the dosage form. (Tr. 393:6-9 (Metz); Tr. 514:4–515:25 (Kibbe); Tr. 692:24–695:10 (Mayersohn).)

PPI Feedback Loop

Defendants also believe that a POSA would have had a reasonable expectation of success using uncoated PPIs because the prior art described a "positive feedback loop"

[22] Defendants dispute the relevance of the data in Pilbrant 1993 because the study reported the bioavailability of a PPI after a meal and commercially available PPIs, even enteric coated ones, are typically administered with food. (Tr. 964:15–965:21.)

that would increase the bioavailability of an uncoated PPI. As explained by both Dr. Kibbe and Dr. Mayersohn, the feedback loop occurs because the first PPI dose inhibits stomach acid production and raises gastric pH, which consequently causes less acid degradation of the second dose, which further inhibits acid production, and so on. (Tr. 492:25–494:18; Tr. 589:9–590:4; 620:18–627:11; DTX-1396 at 6–7.) Dr. Kibbe pointed to Clissold (DTX-1036) as support for this feedback mechanism. (Tr. 492:25–493:25.) Dr. Mayersohn cited Tolman (DTX-1061) as additional evidence of the feedback effect. (Tr. 625:16–627:7.)

Horizon disputes the relevance of Clissold (DTX-1036) and Tolman (DTX-1061), arguing that those references do not assert that an uncoated PPI would increase its own bioavailability over time or reach therapeutically effective levels. (Dkt. 489-1 at 38–39.) Horizon expert Dr. Taft explained that Clissold and Tolman would not provide a POSA with a reasonable expectation of success for an uncoated PPI because those articles evaluated enteric coated or otherwise buffered PPI formulations. (Tr. 1067:9–1068:3.)

Disadvantages of Enteric Coated Formulations

Defendants also submitted evidence that a POSA would have been motivated to use an uncoated PPI because of known disadvantages of enteric coated PPI formulations. (Dkt. 489 at 46–47.) International Patent Pub. No. WO 00/78293 states that "[o]meprazole should preferably not be in contact with the enteric coating" because the enteric coating can cause "discoloration and degradation of omeprazole." (DTX-1105 at 4–5.) On cross-examination, Dr. Williams was presented with U.S. Patent 6,077,541 ('541 patent) (PTX-242) describing how the potential need to provide a protective layer

between PPIs and their enteric coating can "increase[] the length of the manufacturing process and the cost of the product." (Tr. 971:24–973:20.) He agreed that one "wouldn't have that problem" if one "ha[d] a delayed release coat that's not pH-dependent." (Tr. 973:11-16.) The '541 patent also discloses that "[e]nteric coated formulations are expensive and time consuming to manufacture, and requires [sic] elaborate technology and equipment." (Tr. 973:21–974:9.)

2. Secondary Considerations of Non-Obviousness

We also consider the significance and relevance of so-called "secondary considerations" such as commercial success, long felt but unsolved needs, and the failure of others. See AstraZeneca LP v. Breath Ltd., 88 F. Supp. 3d 326, 382 (D.N.J.), aff'd, 603 F. App'x 999 (Fed. Cir. 2015).

(i) *Unexpected results*

Horizon submits that the nonobviousness of the Invention is evidenced by the fact that its Vimovo product had surprising and unexpected results in treating NSAID-related gastrointestinal injury. Dr. Williams and Dr. Johnson testified that the success of a formulation with an uncoated PPI in Vimovo was an unexpected result. (Tr. 782:24–783:6; Tr. 1169:16–1170:1.) In designated deposition testimony, Dr. Sostek of AstraZeneca testified that "it was unexpected that a completely unprotected form of a proton pump inhibitor could result in effective acid suppression." (DTX-1396 at 10.) Dr. Johnson also highlighted statements from certain clinical studies involving Vimovo. (Tr. 1170:2-7.) One such study, Goldstein (DTX-1135), noted "a striking and highly statistically significant difference between the patients that received Vimovo" compared

to other formulations, including those who received enteric coated naproxen alone. (Tr. 1170:22–1172:3.) Another publication, Hawkey (DTX-1142) characterized Vimovo by noting that "Impressively—and surprisingly, in view of the instability of PPIs in gastric acid—a clinical trial has shown a reduction . . . in the proportion of patients developing NSAID-associated gastric ulcers on [Vimovo] compared with similar doses of naproxen alone." (DTX-1142 at 3; Tr. 1087:22–1088:10.)

Defendants dispute the relevance of the Goldstein study because it compared Vimovo against formulations ***without*** a PPI component. (Tr. 1170:20–1171:14.) They submit that the study cannot be considered an "unexpected result" because it does not show the effectiveness of Vimovo against the closest prior art, which they assert would be a Naproxen/PPI co-therapy. (Tr. 350:18–354:8; Tr. 641:5–643:17; DTX-1396 at 10; DTX-1398 at 10–11.)

(ii) *Skepticism*

Horizon argues that the nonobviousness of the Invention is supported by evidence that there was skepticism that the Invention would work. As with its evidence of unexpected results, Horizon's skepticism evidence at trial focused on the Invention's use of an uncoated PPI. Dr. Plachetka, the inventor, testified that potential marketing partners for Vimovo were skeptical about whether an uncoated PPI would work in the formulation. (Tr. 65:5-22; 68:23–70:9.) In one email from a prospective partner (TAP), an employee asked what steps Pozen had taken to address the degradation of a PPI that might be predicted from using an uncoated PPI. (PTX-267 at 1.) Dr. Plachetka testified that some TAP employees "didn't believe" the data presented about the formulation and

thought it would "never work . . . because everybody knows that [PPIs] have to be enteric coated." (Tr. 66:13–67:23.) In another example, a Pozen employee summarized a call with a potential marketing partner (Purdue) and wrote that Purdue "need[ed] a better understanding of why we do not enteric coat the PPI. They feel this is an 'enigma' vs. all the prior art and they are 'not convinced' it is necessary or beneficial to not enteric coat the PPI." (PTX-085 at 1.) In the same email, the employee asked: "How could all the PPI experts be so wrong for so long?" (PTX-085 at 1; Tr. 796:14–797:18.)

Scientists at AstraZeneca, who had developed the PPIs omeprazole and esomeprazole, similarly appeared to express skepticism regarding the use of an uncoated PPI. (See, e.g., PTX-273; PTX-271; PTX-102; PTX-269.) In one internal email chain, AstraZeneca's Dr. Sostek wrote: "I think it is clear, that the current formulation is NOT optimal from an acid suppression standpoint (because of PPI is degradation [sic] in the stomach), but they characterize it as a good first attempt. . . . It could be difficult to explain to physicians why PPI 'protection' is not necessary for this product unlike all other PPIs." (PTX-273 at 4.) At his deposition, Dr. Sostek explained why he thought it would be difficult to explain to physicians why PPI protection is not necessary for Vimovo:

> Well, for years since 2000 and before, since omeprazole was really first approved in '89, so that at this time was over 25 years. And then by this year, Nexium had been around for five years, Prevacid has been around for 10, 15 years. All of the PPI manufacturers had consistently educated physicians that a critical component of proton pump inhibitors was the enteric coat and that you had to protect the PPI from acid degradation. So I guess that I was saying that in light of all that education effort about the importance of an enteric coat the Pozen

> platform does not have an enteric coat, and so that might create an educational challenge for physicians.

(DTX-1396 at 9.)

Horizon submitted a number of other examples of skepticism about the use of uncoated PPIs. One Pozen memo recounted a conversation in which a doctor stated he was "of the school" that PPIs need to be enteric coated. (PTX-266 at 1.) Another email from Novartis asked Pozen to "[p]lease explain the rationale for the PPI in a non-enteric coated form (since PPIs are acid labile)." (PTX-268 at 1.) A due diligence assessment by Pozen questioned whether "unprotected esomeprazole 20 mg BID [will] produce sufficient acid suppression to meet primary endpoint of Phase II study." (PTX-271 at 2.) The FDA appeared to express skepticism that an uncoated PPI would be effective, and asked Horizon to "clarify if immediate release or delayed release esomeprazole will be used" because "[e]someprazole is acid labile . . . [and] therefore, without a proper delivery system it is not clear if the product will result in an intended pharmacological effect." (PTX-84 at 1; Tr. 789:17-23.)

Defense expert Dr. Mayersohn characterized much of Horizon's skepticism evidence as requests for more information rather than skepticism. (Tr. 650:1–662:16.) Regarding Horizon's AstraZeneca documents, Defendants argue that AstraZeneca was actually concerned about a marketing problem because AstraZeneca had spent years telling physicians that an enteric coating was important. (Dkt. 489-1 at 58; DTX-1396 at 9.) AstraZeneca, as Defendants point out, was the patent holder of a combination of enteric coated esomeprazole with an NSAID and had other patents related to enteric coated esomeprazole. (Tr. 939:5–945:4.) More broadly, Defendants contest the

admissibility of Horizon's skepticism evidence on the basis that the documents are from after the priority date. (Dkt. 489 at 56–57.)

(iii) *Licensing*

Horizon argues in its post-trial brief that the licensing of the '907 and '285 patents by AstraZeneca (and the subsequent acquisition of that license by Horizon) is evidence that the asserted claims are not obvious. (Dkt. 489-1 at 53–54.) Defendants contest the relevance of AstraZeneca's license in view of how quickly AstraZeneca sold the rights to Horizon, and disputes that either license "arose out of recognition and acceptance of the patent." See Stratoflex, Inc. v Aeroquip Corp., 713 F.2d 1530, 1539 (Fed. Cir. 1983). Defendants also note that many potential marketing partners declined the opportunity to license and develop the invention. (Tr. 65:14–68:12.) Moreover, AstraZeneca's interest may have had incentives to license the product because of its existing esomeprazole product; as Dr. Plachetka explained, AstraZeneca had requested to use its own esomeprazole product in the formulation. (Tr. 74:5-13.)

(iv) *Long-felt need*

Horizon argues that the prevalence of NSAID-related gastrointestinal injury is additional evidence of non-obviousness. (Dkt. 489-1 at 55.) Horizon expert Dr. Johnson explained that NSAID-induced gastric injury was a significant medical problem at the time of the invention. (Tr. 1118:22–1120:23; PTX-572.) He also testified that various efforts to create safer NSAID therapies (using, *e.g.*, sucralfate, misoprostol, and acid suppression therapies) had not resolved the problem of NSAID-related injuries. (Tr. 1138:4–1139:4.)

Defendants argue that Horizon did not offer any evidence at trial that the Asserted Patents or Vimovo addressed a long-felt but unmet need of reducing the risk of gastric injury associated with long-term NSAID use. Dr. Johnson conceded that he had not opined on whether NSAID-related injuries had declined following the invention. (Tr. 1227:18–1228:18.) Defense expert Dr. Metz testified that the standard of care remains the same today after the release of Vimovo and that he had not seen any reduction in the incidence or severity of NSAID-induced gastropathy. (Tr. 350:4-15.) Defendants also highlighted designated deposition testimony from Dennis McNamara that Vimovo had not been demonstrated as superior to other available co-therapies. (DTX-1398 at 10–14.)

3. Analysis

We turn now to the overarching inquiry of whether Defendants have demonstrated "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009). Answering that question requires us to address: (1) the level of ordinary skill in pertinent art; (2) the scope and content of prior art; (3) differences between the claims and the prior art; and (4) secondary considerations. See KSR Int'l Co., 550 U.S. at 406.

We note preliminarily that the level of ordinary skill in the art was not a significant area of contention between the parties. The parties submitted proposed definitions of a POSA in the pretrial order:

Horizon's Proposed Definition (Dkt. 421 at 10)	Defendants' Proposed definition (Dkt. 421 at 130–31)
A person of ordinary skill in the art for the inventions of the asserted claims is a person with at least a graduate degree in pharmacy, chemistry, chemical engineering, pharmaceutics, or a comparable field, and some relevant pharmaceutical formulation work experience in industry. Other aspects of the claimed subject matter, such as those aspects relating to the amounts of active ingredient in the unit dosage form, would implicate a person skilled in the art of dosage, administration, and intended clinical use and effect of an acid inhibitor. The development of new formulations or dosage forms can require people with different areas of expertise, including, for example, those with familiarity of the dosage and administration of the relevant active ingredients, as well as those with familiarity or experience in drug formulation.	A person of ordinary skill in the art (POSA) is a pharmaceutical scientist having a Ph.D. degree, or equivalent training or degree, and at least 2 years of practical experience in pharmaceutical formulations. A POSA would have collaborated with a medical doctor having at least 2 years of practical experience treating patients in the gastroenterology field and a pharmacologist / pharmacokineticist having a Ph.D. degree, or equivalent training or degree, and at least 2 years of practical experience in pharmacology and pharmacokinetics. A POSA has a general understanding and knowledge of basic principles of formulation development. A POSA is familiar with the general strategies, procedures and tools of pharmaceutical formulation development, including pre-formulation studies, formulation screening and optimization, and experimental design. A POSA is also generally familiar with the commonly used textbooks in the field of formulation development, and has a general knowledge of the relevant references and/or printed publications in the field of pharmaceutical formulation.

Witnesses at trial, to the extent they testified about the definition of a POSA, offered largely similar definitions. (See, e.g., Tr. 268:4–269:8; Tr. 444:15-23; Tr. 574:2-8; Tr. 721:8–722:5; Tr. 1028:14-19.) Importantly for our purposes, experts from both sides testified that differences between the proposed definitions of a POSA did not affect their opinion. (See Tr. 270:13-17 (Dr. Metz); Tr. 574:14-20 (Dr. Mayersohn, noting "they're virtually identical descriptions of persons of ordinary skill"); Tr. 723:13-23 (Dr. Williams); Tr. 1144:23–1145:18 (Dr. Johnson).) We will formally adopt Defendants' definition of a POSA (Tr. 444:13-23), but note that our analysis would be the same under either definition.

The relevant prior art presented by the parties at trial fell broadly into two categories. The first category pertained to drug therapies designed to reduce NSAID-related injury and NSAID/PPI co-therapies. The second pertained to the use and efficacy of coated and uncoated PPIs.[23] We briefly review the key disclosures in the prior art guiding our obviousness analysis.

The '843 (Arthrotec) patent (DTX-1063) disclosed a pharmaceutical composition with an enteric coated NSAID core (*i.e.*, diclofenac or piroxicam) surrounded by a prostaglandin. ('843 patent at col. 12, lines 19–62.) The '519 patent (DTX-1112) disclosed the coordinated release of a prostaglandin and an enteric coated NSAID designed to delay the release of the NSAID in order to protect the stomach. ('519 patent at col. 1, lines 21–30.) The prior art includes studies comparing various treatment options for NSAID-related injuries, including misoprostol, omeprazole, and ranitidine. (DTX-1077; DTX-1069.) Based on these studies, a POSA would have understood that omeprazole compared favorably in at least some ways to misoprostol and ranitidine in preventing NSAID-related injuries. (DTX-1080; DTX-1089.) The prior art also disclosed co-therapies that included PPI and NSAID components. (DTX-1051; DTX-1064; DTX-1118.) Indeed, the '907 patent acknowledges that "others have disclosed strategies for combining" PPIs and NSAIDs for therapeutic purposes. ('907 patent at col. 2, lines 20–27.)

[23] It is undisputed that some features of the Invention were well-known in the prior art, including: (1) use of an NSAID to treat arthritis; (2) use of PPIs to inhibit acid; and (3) use of an enteric coated NSAID. (Tr. 82:13–93:24.)

There is much discussion in the prior art on the importance of protecting PPIs because of their acid lability. The '346 patent (DTX-1117) discloses the use of an uncoated PPI together with a buffering agent designed to protect the PPI from acid degradation. ('346 patent at col. 11, lines 13–23.) One review article states that PPIs are "acid-unstable, requiring protection against gastric acidity." (PTX-337 at 5.) U.S. Patent No. 6,013,281 (PTX-573) notes that "it is obvious that a proton pump inhibitor in an oral solid dosage form must be protected from contact with the acidic reacting gastric juice" and that a dosage of PPIs "is best protected from contact with acidic gastric juice by an enteric coating layer." ('281 patent at col. 4, line 63 to col. 5, line 11.) Another reference discloses that PPIs "are all acid-labile, so when administered orally they ***must be*** formulated in an enteric coating to protect them from rapid degradation in the stomach." (PTX-077 at 3 (emphasis added).)

The prior art also discusses the bioavailability of uncoated omeprazole. Pilbrant 1985 states that a suspension of uncoated PPI had a bioavailability of about 50%. (PTX-435 at 1.) A subsequent study, Pilbrant 1993 analyzed omeprazole absorption after a meal and indicated that bioavailability might be as low as 16%. (PTX-262 at 7–8.) Clissold cites the 44% bioavailability total from Pilbrant 1985 but also explains that the PPI might increase its own bioavailability over time "by decreasing gastric acid secretion and enhancing the extent of its absorption." (DTX-1036 at 19.) Regårdh offers some evidence that the bioavailability of omeprazole might increase as the dosage amount increases. (DTX-1029 at 10–11.)

The prior art contains at least some support for the notion that the use of an enteric coat in a PPI formulation can have some disadvantages, as the enteric coat itself can degrade the PPI. (DTX-1105; PTX-242.)

We find that the Invention departs from formulations disclosed in the prior art in essentially two ways. First, the Invention differs from other coordinated release drug formulations in the prior art for treating NSAID-related gastric injuries (*e.g.*, the '843 patent) because it used a PPI (*e.g.*, esomeprazole) instead of a prostaglandin (*e.g.*, misoprostol) as the agent to prevent or treat NSAID-related gastric injury. Second, the Invention differs from other therapies in the prior art that used PPIs (including NSAID/PPI co-therapies) by virtue of using an uncoated PPI.

We conclude that Defendants have failed to demonstrate that a POSA would have been motivated to combine the teachings of the prior art references and would have had a reasonable expectation of success in doing so. Specifically, based on the evidence presented at trial, we conclude that a POSA would not have been motivated to use an uncoated PPI given numerous prior art references reflecting a widely-held understanding that the acid lability of PPIs, particularly in a solid dosage form, would generally require an enteric coating. See KSR Int'l Co., 550 U.S. at 416 (noting "principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious").

Defendants contend that the prior art demonstrated, at most, that enteric coated PPIs were a superior alternative to uncoated PPIs. (Dkt. 489 at 52.) These arguments understate the language used in the prior art when discussing the need to enteric coat

PPIs. One reference cited the "obvious" need to protect a PPI from acidic gastric juice, and noted that a PPI is "best protected . . . by an enteric coating layer." (DTX-573 at 5–6.) Another explained that "PPIs are highly acid labile and hence oral formulations are enteric coated." (PTX-244 at 2.) Pilbrant 1985—a reference heavily relied upon by Defendants to argue that an uncoated PPI might be expected to work—affirmatively "ruled out" the use of uncoated omeprazole given its relatively low bioavailability. (PTX-435 at 2.) Indeed, the Federal Circuit has previously concluded that Pilbrant 1985 "would discourage a [POSA] from pursuing conventional oral dosage forms such as tablets, capsules, or granules with non-enteric coated PPIs, and thus teaches away from such formulations." Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1355 (Fed. Cir. 2012). Although Defendants' experts argued that a POSA would have been motivated to use an uncoated PPI, prior statements by those same experts undercut the credibility of their testimony. (See, e.g., Tr. 365:6–369:5; Tr. 686:4–689:12.)

In light of the expert testimony and prior art references submitted at trial, we disagree that a POSA would have been motivated to use an uncoated PPI in a new combination drug product. See In re Chapman, 595 F.3d 1330, 1337 (Fed. Cir. 2010) ("A finding that a reference teaches away can preclude a finding that the reference renders a claim obvious.") We acknowledge Defendants' various objections to particular references (Dkt. 489 at 48–50), but conclude that the references in their entirety would have counseled a POSA against the use of an uncoated PPI.

We are not persuaded by Defendants' evidence that a POSA would have had a reasonable expectation that an uncoated PPI would be successful. Defendants base much

of their argument on the 44% bioavailability figure from Pilbrant 1985 and the assertion that a POSA would simply double the dosage to account for acid degradation of the PPI. But Pilbrant 1985 itself ***ruled out*** the possibility of using an uncoated PPI given its low bioavailability. (PTX-435 at 2.) Tellingly, in our view, Defendants' experts could not recall examples where a formulator simply increased the dosage to compensate for low bioavailability caused by acid degradation. (Tr. 393:6-9; Tr. 514:4–515:25; Tr. 692:24–695:10.) And notably, a POSA would be aware that other disclosures, such as Pilbrant 1993, suggest that bioavailability might be even lower than the 44% figure from Pilbrant 1985. (PTX-262 at 7–8.)

Nor are we persuaded by Defendants' contention that a POSA would have had a reasonable expectation of success by virtue of other mechanisms that might serve to increase the bioavailability of uncoated PPI. Although there is some indication from Clissold (DTX-1036) and Tolman (DTX-1061) that there may be a "feedback loop" that might eventually increase the bioavailability of an uncoated PPI, those references did not evaluate whether uncoated PPIs would be effective. The '346 (Zegerid) patent disclosed that an uncoated PPI could be administered with an alkalizing agent such as sodium bicarbonate. But as explained by Horizon's experts, a POSA would have had concerns that the addition of an alkalizing agent would raise new challenges related to tablet size and the possibility that the alkalizing agent would interfere with the enteric coated naproxen also present in the Invention. (Tr. 753:21–760:16.) Indeed, the '346 patent itself describes how sodium bicarbonate can dissolve an enteric coating. ('346 patent at col. 14, lines 32–37.) These drawbacks would have undermined, if not precluded, a

POSA's motivation to use an uncoated PPI or any expectation of success in doing so. See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1365 (Fed. Cir. 2008) (noting that challenges associated with the inventive process that "would have prevented one of ordinary skill in this art from traversing the multiple obstacles to easily produce the invention").

The PTAB has similarly rejected the argument that it would have been obvious to use an uncoated PPI in view of Pilbrant 1985. (PTX-351 at 23–26.) Although the PTAB did not analyze all of the references raised at trial, the thrust of the obviousness argument (there made by Defendant DRL) was similar. Consequently, we are mindful that Defendants' evidence must be scrutinized carefully. See Sciele Pharma Inc. v. Lupin Ltd., 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("[I]t may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered.").

Our conclusion is somewhat strengthened by Horizon's evidence of so-called "secondary considerations" of non-obviousness, although we find that the Defendants have failed to satisfy their burden of showing invalidity even without that evidence. For the most part, Horizon's secondary consideration evidence flows from the Invention's use of an uncoated PPI. There is at least some evidence in the record that the success of a formulation with an uncoated PPI was surprising. Indeed, Hawkey explicitly noted that "Impressively—and surprisingly, in view of the instability of PPIs in gastric acid—a clinical trial has shown a reduction . . . in the proportion of patients developing NSAID-associated gastric ulcers on [Vimovo] compared with similar doses of naproxen alone." (DTX-1142 at 3.)

Defendants reject the relevance of Hawkey, noting that unexpected results "must be shown to be unexpected compared with the closest prior art." In re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991). We agree that "naproxen alone" is not the closest prior art, but also note that the reference is commenting on the unexpected result of an uncoated PPI compared, at least implicitly, against PPI formulations in the prior art protected from gastric acid (*i.e.*, through an enteric coat).

Horizon also presented a substantial amount of evidence that industry participants were skeptical that an uncoated PPI would work at all. One potential development partner wrote that they "need[ed] a better understanding of why we do not enteric coat the PPI. They feel this is an 'enigma' vs. all the prior art and they are 'not convinced' it is necessary or beneficial to not enteric coat the PPI . . . How could all the PPI experts be so wrong for so long?" (PTX-085 at 1.) These documents, as well as others outlined above and presented at trial, evince skepticism that a formulation with an uncoated PPI would work. Defendants object to the applicability of these documents because they post-date the Invention and therefore "fail[] as a matter of law." (Dkt. 489 at 56–57.) See In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (identifying "skepticism of skilled artisans ***before the invention***" as a secondary indicium (emphasis added)). We disagree that controlling case law prohibits our consideration of documents created after the priority date when evaluating evidence of industry skepticism. While the relevant inquiry may be whether there was skepticism before or at the time of the invention, we see no reason why post-invention documents cannot be considered as evidence of pre-existing industry skepticism. Accordingly, although we may discount the weight of

skepticism evidence created some time after the invention, documents evincing longstanding skepticism (*e.g.*, an industry participant asking "[h]ow could all the PPI experts be so wrong for so long?") still support our finding of nonobviousness.[24]

Other secondary indicia cited by Horizon do not similarly support a finding of nonobviousness. We do not find that evidence of "licensing" supports a finding of nonobviousness here, in part because the minimal evidence presented by Horizon does not demonstrate that the "licenses arose out of recognition and acceptance of the patent." Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1539 (Fed. Cir. 1983). Likewise, Horizon did not present evidence at trial that the introduction of Vimovo satisfied a "long-felt, but unmet need" by meaningfully reducing the number of injuries associated with NSAID use. (Tr. 1227:18–1228:18) Indeed, Defendants presented unrebutted testimony that the standard of care has remained essentially unchanged. (Tr. 350:4-15.) It is also well-established that filing of an ANDA does not constitute "copying" for obviousness purposes. Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013).

For the reasons above, we conclude that the Defendants have failed to satisfy their evidentiary burden to demonstrate that the Asserted Patents are invalid as obvious.

B. Enablement

Defendants argue that the asserted claims are invalid under 35 U.S.C. § 112 because the '907 and '285 patents do not adequately disclose the utility of using an

[24] Defendants also lodged a standing objection at trial to Horizon's skepticism evidence as inadmissible hearsay, but did not elaborate in their post-trial brief. (Dkt. 489 at 57 (submitting only that Horizon's "vague, after-the-fact, and anecdotal claims derived from hearsay do not salvage the patents").) We deny this objection, but, as noted above, our ultimate conclusion on invalidity would remain the same even without Horizon's evidence of secondary considerations of nonobviousness.

uncoated PPI. (Dkt. 489 at 69.) They highlight that the patents do not contain any experimental testing data regarding the use of uncoated PPIs, and argue that the inventor's unsupported "suspicion" that the invention would work is insufficient to satisfy the utility prong of enablement. (Id.) Horizon responds that the utility of the invention was self-evident to a POSA and that enablement does not require the disclosure of experimental test results. (Dkt. 489-1 at 67.)

There appears to be no serious dispute between the parties that the Asserted Patents disclose how to make and use the claimed invention. Horizon expert Dr. Williams testified that making the claimed formulations would be routine. (Tr. 809:24–819:13.) Defense expert Dr. Mayersohn agreed that the patent specification teaches how to make the claimed tablets. (Tr. 680:18-21.) The patents themselves disclose their intended use. (See, e.g., '907 patent at col. 4, lines 18–27 ("The invention includes methods of treating a patient for pain, inflammation and/or other conditions . . . Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with osteoarthritis or rheumatoid arthritis . . . .").)

Defendants' specific enablement challenge focuses on whether the patents disclose sufficient evidence to support the Invention's claimed utility for treating various medical conditions. (Dkt. 489-2 at 69–70.) They rely primarily on Rasmusson v. SmithKline Beecham Corp. to argue that the disclosures in the '90 7 and '285 patents are inadequate. 413 F.3d 1318, 1324 (Fed. Cir. 2005). Rasmusson involved an enablement challenge to a patent claiming the use of finasteride to treat prostate cancer. Id. at 1322. The Federal Circuit

upheld a finding by the Board of Patent Appeals and Interferences[25] that the claim was not enabled because "a person of ordinary skill in the art would have had no basis . . . for believing that finasteride could be used to treat prostate cancer in light of the state of the art and in light of [the patentee's] failure to provide any data to demonstrate the effects of finasteride in treating prostate cancer." Id. The Federal Circuit cited the Board's review of the scientific articles and expert testimony, and noted that the patentee "did not make any contrary showing that a [POSA] . . . would have recognized that a selective 5αR inhibitor in general, or finasteride in particular, would be effective in treating prostate cancer." Id. at 1324.

The stated utility in the Asserted Patents of using an NSAID and a PPI to treat pain and NSAID-related gastric injury rests on far firmer evidentiary ground than the novel cancer treatment in Rasmusson. Testimony from both sides at trial indicated that a POSA at the time of the invention would have accepted that a combination of an NSAID and a PPI would be effective for treating pain and conditions like arthritis. (Tr. 562:14–563:4; Tr. 1172:12–1173:5.) Given the understood utility of the invention, we disagree with Defendants that the asserted claims constitute "little more than respectable guess" that must be invalidated under the enablement requirement. Rasmusson, 413 F.3d at 1325. We also do not find that a lack of testing data on the efficacy of uncoated PPIs renders the claims invalid. While it may often be true that "patent applications claiming new methods of treatment are supported by test results," it is also "clear that testing need not

[25] The Board of Patent Appeals and Interferences was replaced by the PTAB under the terms of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

be conducted by the inventor." In re '318 Patent Infringement Litig., 583 F.3d 1317, 1324 (Fed. Cir. 2009). Indeed, were testing data required to obtain patents, "the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue . . . potential cures." Id. (citing In re Brana, 51 F.3d at 1568). Consequently, we conclude that Defendants have failed to meet their evidentiary burden to show by clear and convincing evidence that the patents should be invalidated for lack of enablement.

C. Written Description (Uncoated PPI)

Defendants mount a separate written description challenge based on the alleged failure of the '907 and '285 patents to adequately describe the use of uncoated PPI. They believe they have caught Horizon in a catch-22:

> According to [Horizon], the claimed formulation is novel because a POSA would not have expected an uncoated PPI to be effective. Against this background, Plaintiffs argue that a POSA reading the asserted patents' formulation recipes would immediately understand that an uncoated PPI is effective—even though the specifications disclose no data, reasoning, or other information in support. But both cannot be true. Fundamentally, because the patents lack any disclosure of an uncoated PPI's efficacy, the claims are either obvious (if the POSA understands that uncoated PPIs work), or lacking description (if the POSA believes uncoated PPIs would not work).

(Dkt. 489 at 69.)

As Defendants point out, the Asserted Patents do not address the efficacy of uncoated PPIs through experimental testing data or other statements in the specification. (Tr. 666:16–677:14; Tr. 1004:16–1005:11.) Instead, Defendants characterize the specification as "parroting claim language," which they view as insufficient given

Horizon's position that the prior art had taught away from the use of uncoated PPIs. (Dkt. 489 at 66.)

Horizon responds that the specifications of the Asserted Patents adequately describe the use of uncoated PPIs, and that the law does not require the specification to "present data or an explanation of why the prior art was wrong to refute the teaching the in the prior art." (Dkt. 489-1 at 65.) Instead, Horizon cites Allergan, Inc. v. Sandoz Inc., for the proposition that "[a] claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described." 796 F.3d 1293, 1309 (Fed. Cir. 2015).

Our inquiry is whether the lack of information regarding the efficacy of uncoated PPIs means that the patent specification does not "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." Ariad, 598 F.3d at 1351. The '285 patent specification contains various disclosures describing the immediate release of an acid inhibitor as a component of the invention.[26] For example, the specification describes that "[t]he acid inhibitor is in one or more layers outside of the core which do not contain any NSAID. These layers are not surrounded by an enteric coating and, upon ingestion of the tablet or capsule by a patient, release the acid inhibitor into the patient's stomach." ('285 patent at col. 4, lines 37–41.) This early release of the acid inhibitor is repeatedly described, with the specification similarly

[26] As noted above, the '285 and '907 patents contain virtually identical specifications and our analysis applies equally to both patents.

disclosing that: "the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen." (Id. at col. 4, lines 45–51; see also id. at col. 5, lines 12–16.) The immediate release of an uncoated acid inhibitor is explicitly distinguished in the specification from enteric coated PPI formulations that delay the absorption of the acid inhibitor: "[t]he effect [of PPIs] may be diminished towards the end of the usual dosing interval. Intragastric pH rises particularly slowly with the first dose in a course of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours." (Id. at col. 2, lines 3–8.) In contrast, the examples in the specification describe, *e.g.*, the "rapid[] release" of uncoated omeprazole. (Id. at col. 16, lines 33–49.)

Particularly in light of disclosures in the specification describing the immediate release of an uncoated PPI and the potential disadvantages of enteric coated PPI formulations, we conclude that Defendants have not shown by clear and convincing evidence that the Asserted Patents should be invalidated for failing to meet the written description requirement. The lack of experimental testing data or detailed analysis on why an uncoated PPI might prove effective does not require us to find otherwise. We reject, however, Horizon's suggestion that the efficacy of uncoated PPIs need not be described because it is "necessarily inherent" in a formulation. (Dkt. 489-1 at 65.) Horizon relies without elaboration on Allergan, 796 F.3d at 1309, a case which we have previously noted does not provide clear guidance on what qualifies as an inherent property of a formulation nor how that determination bears on the written description

analysis. See Helsinn Healthcare S.A. v. Dr. Reddy's Labs., Ltd., No. 12-2867, 2017 WL 631899, at *26 n.43 (D.N.J. Feb. 14, 2017).

V. Conclusion

For the reasons discussed in Section III, we find that the DRL ANDA II Product infringes claims 1, 2, 3, and 4 of the '285 patent and that those claims are not invalid under 35 U.S.C. § 112. For the reasons discussed in Section IV, we find that the claims of the '907 and '285 patents are not invalid under 35 U.S.C. § 103 or § 112. We will file this memorandum opinion under temporary seal and order the parties to submit a proposed form of Judgment in accordance with this opinion.

s/ Mary L. Cooper
MARY L. COOPER
United States District Judge

Dated: July 10, 2017